DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 27, 2011 has been entered.

Claim Status

2. Claims 2-10, 12-35, 37-41, 44-81 and 89 are cancelled. Claims 1, 11, 36, 42-43, 82-88 and 90-96 are under consideration in this Office Action.

Response to Arguments

3. Applicant's arguments filed April 27, 2011 have been fully considered but they are not persuasive.

Previous Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 11, 36, 42-43, 82-88 and 90-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al., (PNAS, 1999. Vol. 96(22): 12833-12838) in view of Cao et al., (Mol. Microbio. 2002. Vol. 45(5): 1267-1276).

The claims are drawn to a method for determining the mode of action of an antimicrobial compound. Wilson et al., teach exploring drug (the antimicrobial compound) induced alterations in gene expression in *Mycobacterium tuberculosis* by microarray hybridization (title). Wilson et al., conclude the observation that the INH response profiles were distinct from profiles obtained from bacteria exposed in a similar manner to a variety of different toxic compounds, including hydrogen peroxide, ethanol, and aminoglycoside antibiotics (page 12,838). Cao et al., teach comparing *M. tuberculosis* to various antibiotics (page 1273, col.1).

The claims recite detecting hybridization complexes formed by contacting at least one nucleic acid sample, in the presence of at least one sub inhibitory amount of an antimicrobial compound. Wilson et al., teach growth and drug treatment of bacterial M. tuberculosis strains wherein cultures were treated with 0.2ug/ml for INH (page 12384). Wilson et al., teach techniques for microarray hybridization and data analysis at page 12,385, see also Figure 2 showing INH-induced mRNA expression profiles monitored by microarray hybridization analysis (page 12,285). Cao et al., teach detecting hybridization complexes formed by contacting at least one nucleic acid sample (page 1274, col. 2).

The claims recite obtained by culturing bacterial cells in the presence of at least one sub inhibitory amount of an antimicrobial compound having an unknown mode of action. Wilson et al., teach culturing, growth and drug treatment of the bacterial strains with the drug (page 12,834). Cao et al., teach culturing *B. subtilis* strains for DNA microarray analysis (page 1274, col. 2).

The claims recite using a plurality of nucleic acid sequence corresponding to genes of the bacterial cells. Wilson et al., teach the preparation of DNA microarrays which contains genomic sequences and fragments on a substrate (page 12,834). Cao et al., teach using a plurality of nucleic acid sequence corresponding to genes of the *Bacillus subtilis* cells, wherein the plurality of nucleic acid sequences is contained on a substrate (page 1274, col. 2).

The claims recite wherein the plurality of nucleic acid sequences is contained on a substrate, wherein the presence, absence or change in the amount of the hybridization complexes detected. Wilson et al., teach microarray hybridization where the DNA was applied to the array in a hybridization mixture containing genomic sequences and fragments thereby allowing hybridization to occur (page 12,835). Cao et al., teach the plurality of nucleic acid sequences is contained on a substrate (page 1274, col. 2).

The claims recite comparing with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the bacterial cells cultured in the absence or presence of a standard compound having a known mode action. Wilson et al., teach that this system provides the framework for

interpreting the transcriptional responses that we would detect by the microarray hybridization and allow for comparison with published results of genes and proteins that are known to be INH induced (page 12,833). Wilson et al., teach the results show that the characteristic drug response is the result of intracellular conditions associated with the drugs mode of action (page 12,838). Cao et al., teach detecting and quantifying the presence, absence or change in the amount of the hybridization complexes, and comparing with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the *Bacillus subtilis* cells cultured in the absence or presence of a standard compound having a known mode action, is indicative of the similarity or dissimilarity of the mode of actions of the antimicrobial compound and the standard compound using data analysis software (page 1274, col.2).

The claims recite presence or absence of the compound being indicative of the similarity or dissimilarity of the mode of actions of the antimicrobial compound and the standard compound. Wilson et al., teach the detection of hybridization complexes formed by contacting at least one nucleic acid with a plurality of nucleic acid sequences corresponding to genes of the bacterial cells (page 12,835). Cao et al., teach comparing with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the *Bacillus subtilis* cells as indicative of the similarity or dissimilarity of the mode of actions of the antimicrobial compound and the standard compound using data analysis software (page 1274, col.2).

Response to Arguments

5. Applicant's arguments filed April 27, 2011 have been fully considered but they are not persuasive.

Applicants argue that the teachings of Wilson are incorrect and not supported by the record. However as previously stated, the teachings of Wilson in view of Cao are well founded.

Applicants argue that 0.02ug of INH per ml is not an example of a sub-inhibitory amount. Applicants asserts that Wilson *et al.,* does not teach the subinhibitory amount limitation because Wilson et al., *Mycobacterium tuberculosis* to isoniazid (INH) at concentrations of 0.2 μg of INH per ml, which are above the minimum inhibitory concentration of INH. The definition of subinhibitory amount within the instant specification at Pages 11-12, lines 35-3. A review of subinhibitory amounts of INH with Mycobacterium tuberculosis by Sundaram et al., (Biochemical and Biophysical Res. Comm. 1977. Vol. 78(2):839-8485) states that drug exposure was inhibited mildly by 0.1 μg /ml and 0.2 μg /ml concentration and completely by 0.3 μg /ml. However the MIC was 0.5 μg /ml. Therefore the subinhibitory amount of Wilson, using the same antibiotic and the same bacterial species shows that the 0.2 μg/ml is a subinhibitory amount of antibiotic contrary to applicants' assertions.

Additionally 0.02 ug of INH merely respects an example of a subinhibitory amount, and does not limit the claims. Therefore, the fact that Wilson et al., teach other amounts of INH, which also do not kill the bacteria means that Wilson et al., meets the subinhibitory limitation of the claims. Contrary to Applicants' assertion, Wilson et al.,

teach amounts that result in bacterial growth. As Applicants have previously stated, the subinhibitory amounts would be amount below the minimum inhibitory concentration, and would not kill the bacteria but show signs of growth. Wilson et al., teach concentrations of 0.2 μg of INH per ml, where growth occurs and the bacteria is not killed as evidenced by the INH-induced expression profiles. Thus, Wilson et al., meets the sub-inhibitory limitation of the claims.

Applicants assert that Applicants have not optimized the inhibitory range of an antimicrobial compound but have submitted methods that produce unexpected results. However, it is the position of the Office that growth of bacterium exposed to subinhibitory amounts of antibiotic is not unexpected. It was well known in the art that by drug exposure at subinhibitory 0.1 μg /ml and 0.2 μg /ml concentration mildly effected growth of the bacteria. The prior art also already teaches detecting hybridization of complexes obtained by cultured cells in the presence of a subinhibitory amount of antibiotic. Wilson et al., teach comparing the changes of hybridization complexes detected as being indicative of the similarity of modes of actions of antimicrobial compounds. Therefore this argument is unpersuasive.

Applicants urge that the use of sub-inhibitory concentrations consequently slows the action of the compounds, and limits the expression of genes that are correlated to secondary effects, allowing a predominance of expressed nucleic acids that correlate with the activity of the antimicrobial compound, which is related directly, and primarily, with its mode of action on the cell and submit that their results exhibit a superior advantage that a person skilled in the art would have found surprising

and unexpected. Wilson et al., teach that the results induced by INH suggest expression profiles providing a characteristic signature that is specific for the cellular process that is affected by the compound; thus Wilson et al., also teach allowing a predominance of expressed nucleic acids that correlate with the activity of the antimicrobial compound. Wilson et al., their results show the result of intracellular conditions associated with the drug's mode of action because the bacteria encodes proteins relevant to the drug's mode of action; thereby limiting the expression based on the compounds effects.. Therefore, like Wilson, the instant claims correlate with the activity of the antimicrobial compound, which is related with its mode of action on the cell. Wilson et al., teach intracellular conditions are characteristic of the drugs activity and the ability to identify novel compounds that exert similar effects. Therefore applicants' assertion that unexpected results were not found persuasive.

Therefore it would have been prima facie obvious at the time of applicants' invention to apply the *Bacillus subtilis* strain of Cao et al., to Wilson et al., method for determining the mode of action of an antimicrobial compound in order to provide obtain antimicrobial mode of action results for *B. subtilis* which is known to be resistant to known antimicrobial drugs.

Wilson et al., clearly and specifically teach the growth and drug treatment of the strain wherein cultures grown and treated with 0.2ug/ml the antimicrobial compound which meet the limitations of subinhibitory amounts contrary to Applicants assertions. Therefore Applicants' argument is not persuasive and the rejection is maintained.

Conclusion

6. No claims allowed.

7. This is a Request for Continued Examination applicant's earlier Application No. 10/656,055. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Gary Nickol, can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645